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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,373	06/21/2002	Isao Ishida	051023-0115	3667

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FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,373	ISHIDA ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6 and 9-25* is/are pending in the application.

4a) Of the above claim(s) *6 and 10-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-5, 9, 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Response, filed 12/19/05, has been entered. Claims 1, 5, 9 and 25 are amended; claims 1, 3-6, 9-25 are pending; claims 6 and 10-24 are withdrawn; claims 1, 3-5, 9 and 25 are under current examination.

Election/Restrictions

Claims 6 and 10-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/4/04.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 9 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons of record, advanced in the Office action, mailed 10/5/05.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The specification teaches working examples, wherein the human chromosome 7 fragment, designated E22, is used to produce chimeric mice. See Examples, 1 and 4, for example. Particularly, the specification cites the method of WO 97/07671, to produce a mouse A9 cell library, harboring various human chromosomes. The '671 document is in Japanese, however, the Examiner notes that Tomizuka *et al.* (**Nature Genetics**, 16: 133-143 (1997), cited as Document A6 on Applicants' IDS, filed 6/21/02), teaches the general methodology of the production of chimeric mice expressing particular human chromosomes. In particular, they teach the microcell mediated-chromosome transfer method (MMCT) that is taught in the instant specification. See Figure 1. MMCT relies upon the spontaneous fragmentation of human chromosomes by irradiation, and the isolation of the resultant fragments and identification of the fragments by PCR (see pp. 140-141, Methods & Materials). The instant specification teaches the generation of the E22 fragment by this MMCT method, and use of this particular fragment to produce chimeric mice.

As the E22 fragment is essential to the claimed method, it must be obtainable in a repeatable method set forth in the specification or otherwise be readily available to the public. If the E22 fragment is not so obtainable or available, the requirements of 35 U.S.C. 112, regarding "how to make" may be satisfied by a deposit of the E22 fragment. The specification does not disclose a repeatable process to obtain the E22 fragment because it teaches the generation of the fragment by spontaneous fragmentation by irradiation, and it is not apparent if it is readily available to the public. If Applicants feel that the production of E22 fragment is disclosed by a repeatable process, Applicants are invited to point to specific support in the specification by page and line number.

If the deposit is to be made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the E22 fragment has been deposited under the Budapest Treaty and that the E22 fragment will be

irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement.

It the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request of for the effective life of the patent, whichever is longer; and,

(d) a test of viability of the biological material at the time of deposit (see 37 CFR 1.807);

and,

(e) the deposit will be replaced if it should ever become inviable.

Once the deposit has been perfected, the claims will be limited to the E22 fragment.

Applicants' Arguments. Applicants argue that, with regard to the prior rejection, that it is not at issue whether E22 *per se* can be repeatedly produced, but rather, whether the specification teaches a non-spontaneous method for producing *any* chromosome fragment that contains a CYP3A4 gene. Applicants argue that E22 is not the only chromosome fragment disclosed by the specification, and it is unnecessary and inappropriate to limit Applicants' invention to the E22 fragment. Applicants argue that the instantly claimed mouse is useful for *in vivo* evaluation of

drug metabolism, because cytochrome genes mediate the way in which the body processes pharmaceuticals. Applicants argue that the specification provides two basic fragmentation methods – irradiation based spontaneous fragmentation and site-specific fragmentation. Thus, the prior rejection only relies on irradiative fragmentation, and Applicants argue that precise truncation of a human chromosome to obtain a fragment is also disclosed. See pages 6-7 of the Response.

Response to Arguments. These arguments are considered, but not persuasive. The prior rejection is directed, specifically, to the generation of the E22 fragment, not to the general methodology of producing fragments, as asserted by Applicants. The mouse that is instantly claimed, and any of its resultant phenotypes, is dependent upon the fragment used. See also, prior Office actions, for example, pages 4-5 of Office action, mailed 8/31/04; pages 9-10 of the Office action, mailed 2/25/05. The E22 fragment is considered essential to the claimed invention, and the fragment *itself* must be disclosed in a repeatable process in order to fulfill the requirements of "how to make", under 112, 1st paragraph.

Applicants' Arguments. Applicants' argue that the Ohshima Declaration, previously submitted, show that producing mice with human chromosome fragments that comprise a CYP3A4 gene, and then breeding a chimeric mouse using the selected cell. Applicants argue that while the specific E22 fragment is obtained by irradiation-mediated fragmentation, the fragment shown in the Declaration is obtained by specific cleavage. Thus, Applicants argue that the Declaration was provided in response for evidence demonstrating the repeatability of *any* disclosed fragmentation method, and this Declaration provides evidence to show that this is possible, and further, that Dr. Ohshima did not set out to reproduce the *exact* chromosome fragment, but that this shows that the methodology is repeatable and that the Ohshima fragment is obtained from methodology that differs from that which is used to obtain the E22 fragment. See page 8 of the Response. Applicants state that the Ohshima fragment was produced by truncating human chromosome

7, specifically at a telomere site introduced at the AF006752 locus. The fragment was created from the DF141 fragment, which was obtained by deliberately inserting a telomere sequences at the AF006752 site of the human chromosome. The Ohshima fragment was created by introducing a loxP site into the AC004922 site of the DF141 and then cleaving it at the loxP site. Applicants argue that this shows the site-specific cleavage of the H5 clone, which harbored full length human chromosome, described in Example 14. Thus, Applicants argue that this fragment and the Example 23 fragment each comprise portions of human 7 and 14 chromosomes. See pages 8-9, bridging ¶. Applicants argue that the claim requires only the presence of any human chromosome fragment that is not integrated into the mouse cell genome, wherein the human chromosome fragment expresses at least one human cytochrome CYP3A4 family gene. Applicants argue that the mouse produced by Dr. Ohshima meet this requirement, because these mice have the CYP3A4, CYP3A5, and CYP3A7 genes at the chromosome fragment disclosed in the specification. Thus, Applicants argue that this fragment can be created either by telomere truncation, or by the irradiation-mediated fragmentation methods. See page 10.

Response to Arguments. These arguments are considered, but not persuasive. The prior rejection is directed to the reproducibility of a particular fragment, E22, which is essential to the claimed invention. The mice of the instantly claimed invention, are produced using this fragment, and thus, their phenotype is directly correlated to the expression of the genes on this fragment. Although, as shown in the Ohshima Declaration, that one could possibly produce other fragments, which contain other family genes, one, given the art at the time of filing, could not predict how these other genes (or any other genes associated with a different fragment) would affect the resultant phenotype. Thus, one of skill in the art could not use these mice, as stated in the prior Office action.

Applicants' Arguments. Applicants' state that, in the prior Office action, the Examiner questions whether the phenotype of the mouse produced by the inventive method is the same as the claimed mouse, because the mice of Example 23 have an additional chromosome fragment, #14, SC20. Applicants argue that this example teaches the translocation of the SC20 fragment to the chromosome 7 fragment. Applicants argue that the inventors employed chromosome 7 and 14-specific probes to confirm that signals derived from both probes were observed on the same chromosome, and the resultant chromosome were subsequently used in examples 24-26. Applicants argue that the Examiner has erroneously interpreted the observed rifampicin-induced phenotype as a direct consequence of two distinct fragments, when, in actuality, the phenotype results sole from the chromosome 7 fragment. Applicants point to Example 4 to show that the cells of the liver and small intestine of the claimed mouse can be induced by rifampicin to express CYP3A4. See pages 10-11. Applicants argue that this does not mean that other chromosomes are excluded from the cell of the claimed mouse, because the claim states that it "comprises", and indeed, other chromosomes do exist in the cell of the claimed mouse, including its own endogenous chromosomes. Applicants argue that the specification fully supports and enables the claimed invention. See page 11 of the specification.

Response to Arguments. Applicants' arguments are considered, but not fully persuasive. As stated previously, the instantly claimed invention is not enabled because the claims fail to recite an appropriate phenotype for the instantly claimed mice, such that one of skill in the art could use the mice. Furthermore, one of skill in the art could not rely upon the state of the art with regard to the phenotype of these mice. The specification provides a working example that shows that the mouse's cells are inducible by rifampcin. The claims fail to reflect this phenotype. Thus, absent any phenotype, one could not use these mice.

Accordingly, in view of the lack of teachings or guidance provided by the specification, with regard to the production of human chromosome fragments which express at least one human cytochrome CYP3A4 family gene, other than the exemplified fragment, E22, would have required undue experimentation for one of skill in the art to practice the claimed invention.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tnt
Thaian N. Ton
Patent Examiner
Group 1632

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER